(FILE 'HOME' ENTERED AT 10:21:52 ON 21 SEP 2005)

FILE 'MEDLINE' ENTERED AT 10:22:01 ON 21 SEP 2005

L1	22	S	(266 OR MAB266 OR M266 OR AB266) AND AMYLOID?
L2	13	S	AMYLOID? AND (13-28 OR 16-24)
L3	1363	S	IMPROV? (5A) COGNITI? AND (ALZHEIMER? OR DOWN? OR IMPAIR?)
L4	1059	S	L3 AND PY<2004
L5	71	S	L4 AND AMYLOID?
L6	5	S	L5 AND REVIEW

ANSWER 37 OF 71 MEDLINE on STN
AN 2001125789 MEDLINE
DN PubMed ID: 11135604
TI **Amyloid** beta vaccination: reduced plaques and **improved cognition**.
AU Younkin S G
CS Center for Neuroscience, Mayo Clinic Jacksonville, Jacksonville, Florida, USA.. younkin.steven@mayo.edu
SO Nature medicine, **(2001 Jan)** 7 (1) 18-9.
Journal code: 9502015. ISSN: 1078-8956.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200102
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010222
AB Studies in three different transgenic mouse models suggest that the **amyloid** beta-protein contributes to memory loss in **Alzheimer** disease. Immunization with an **amyloid** beta-peptide fragment reduces learning and memory **impairments** in mice, and this approach may eventually be used to prevent and/or treat this disease in people.

L2: Entry 11 of 11 File: USPT Sep 7, 2004

DOCUMENT-IDENTIFIER: US 6787138 B1 09/723,927 division of 09/201,430
** See image for Certificate of Correction **
TITLE: Prevention and treatment of amyloidogenic disease

Primary Examiner (1):
Scheiner; Laurie

INVENTOR (1):
Schenk; Dale B.

Other Reference Publication (240):
Younkin, "Amyloid .beta. vaccination; reduced plaques and improved cognition," Nature Medicine, 7:18-19 (2001).

ANSWER 3 OF 5 MEDLINE on STN
AN 2002690364 MEDLINE
DN PubMed ID: 12450488
TI **Alzheimer**'s disease and the basal forebrain cholinergic system: relations to beta-**amyloid** peptides, cognition, and treatment strategies.
AU Auld Daniel S; Kornecook Tom J; Bastianetto Stephane; Quirion Remi
CS Douglas Hospital Research Centre, 6875 Blvd Lasalle, Verdun, Que, Canada H4H 1R3.
SO Progress in neurobiology, **(2002 Oct)** 68 (3) 209-45. Ref: 504
Journal code: 0370121. ISSN: 0301-0082.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200303
ED Entered STN: 20021214
Last Updated on STN: 20030306
Entered Medline: 20030305
AB **Alzheimer**'s disease (AD) is the most common form of degenerative dementia and is characterized by progressive **impairment** in cognitive function during mid- to late-adult life. Brains from AD patients show several distinct neuropathological features, including extracellular beta-**amyloid**-containing plaques, intracellular neurofibrillary tangles composed of abnormally phosphorylated tau, and degeneration of cholinergic neurons of the basal forebrain. In this **review**, we will present evidence implicating involvement of the basal forebrain cholinergic system in AD pathogenesis and its accompanying cognitive deficits. We will initially discuss recent results indicating a link between cholinergic mechanisms and the pathogenic events that characterize AD, notably **amyloid**-beta peptides. Following this, animal models of dementia will be discussed in light of the relationship between basal forebrain cholinergic hypofunction and cognitive **impairments** in AD. Finally, past, present, and future treatment strategies aimed at alleviating the **cognitive** symptomatology of AD by **improving** basal forebrain cholinergic function will be addressed.

ANSWER 71 OF 71 MEDLINE on STN

AN 91288308 MEDLINE

DN PubMed ID: 2062728

TI The treatment of cognitive **impairment** in **Alzheimer**'s disease: beyond the cholinergic approach.

AU Davidson M; Stern R G

CS Department of Psychiatry, Mt. Sinai School of Medicine, New York, New York.

SO Psychiatric clinics of North America, **(1991 Jun)** 14 (2) 461-82.
Ref: 175
Journal code: 7708110. ISSN: 0193-953X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LA English

FS Priority Journals

EM 199108

ED Entered STN: 19910825
Last Updated on STN: 19980206
Entered Medline: 19910802

AB Despite the well-founded rationale for the use of cholinomimetic and monoaminergic agents in the treatment of **Alzheimer**'s disease, thus far, these strategies have only led to modest results. None of the drugs assessed to date have been shown to **improve cognitive** function to a clinically significant degree in patients with **Alzheimer**'s disease. Some agents have produced mild improvements on specific tests, whereas others seem to slow **down** the progression of the disease. This article provides a brief overview of the current trends in the treatment of cognitive dysfunction in **Alzheimer**'s disease.

ANSWER 70 OF 71 MEDLINE on STN
AN 93299755 MEDLINE
DN PubMed ID: 8518999
TI Nimodipine: cognition, aging, and degeneration.
AU de Jonge M C; Traber J
CS Institute for Neurobiology, Troponwerke, Cologne, Germany.
SO Clinical neuropharmacology, **(1993)** 16 Suppl 1 S25-30. Ref: 44
Journal code: 7607910. ISSN: 0362-5664.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199307
ED Entered STN: 19930813
Last Updated on STN: 19930813
Entered Medline: 19930729
AB Over the years, it has become apparent that many cytotoxic events employ a common pathway in destroying cells, namely the disruption of calcium homeostasis. Further studies show that the aging process is also accompanied, perhaps even partly caused, by changes in cellular calcium regulation. Finally, initial evidence has appeared in the literature showing that the **Alzheimer** beta-**amyloid** protein also interferes with calcium homeostasis. In these situations, the use of calcium antagonists, such as nimodipine, is expected to prevent part of the damage resulting from disrupted calcium regulation. Indeed, studies with nimodipine show that the compound reduces neuronal degeneration in a variety of toxic conditions. In addition, the compound has a functional effect in that it increases spontaneous neuronal firing of aged neurons, presumably by reducing the age-dependently increased afterhyperpolarization. Nimodipine also reduces age-related perivascular anomalies and increases cerebral blood flow. A combination of these effects is probably why the substance is found to **improve cognition** in aged animals and in aged humans with **impaired** brain function.

ANSWER 67 OF 71 MEDLINE on STN
AN 95283635 MEDLINE
DN PubMed ID: 7763338
TI Cholinergic therapies for **Alzheimer**'s disease. Palliative or disease altering?.
AU Davis R E; Doyle P D; Carroll R T; Emmerling M R; Jaen J
CS Applied Genetics, San Diego, California, USA.
SO Arzneimittel-Forschung, **(1995 Mar)** 45 (3A) 425-31. Ref: 45
Journal code: 0372660. ISSN: 0004-4172.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199506
ED Entered STN: 19950707
Last Updated on STN: 19980206
Entered Medline: 19950629
AB Loss of cholinergic function in the neocortex and hippocampus arising from death or atrophy of basal forebrain cholinergic neurons is a consistent feature of the **Alzheimer** brain at autopsy or biopsy. Replacement of lost cholinergic function, therefore, may be of therapeutic benefit to the **Alzheimer**'s (AD) patients. This can be accomplished by enhancing endogenous levels of acetylcholine (ACh) through inhibition of its degradation by acetylcholinesterase on by directly mimicking its actions at postsynaptic muscarinic receptors. Initial efforts focused on inhibition of cholinesterase activity with tacrine (1,2,3,4-tetrahydroaminoacridine monochloride, CAS 1684-40-8, THA, Cognex). Tacrine is a mixed, reversible inhibitor of cholinesterase activity that binds near but not to the catalytically active serine in the active site of the enzyme. Through this action tacrine indirectly elevates ACh levels in the brains of animals and **improves cognitive** performance in rodents and monkeys. More importantly, tacrine has been shown to significantly **improve** several measures of **cognitive** performance in probable AD patients in well-controlled clinical trials, although not all patients respond to this agent. CI-979 ((E)-1,2,5,6-tetrahydro-1-methyl-3-pyridine-carboxyaldehyde-O-meth yl oxime, CAS 139886-04-7) is a non-subtype selective, partial muscarinic agonist that enhances cognitive performance and increases central cholinergic activity in rodents at doses below those required to increase peripheral cholinergic tone. In normal healthy volunteers, CI-979 is well tolerated at single and multiple doses (q 6 h) up to 1.0 mg. In normal healthy volunteers, CI-979 is well tolerated at single and multiple doses (q 6 h) up to 1.0 mg. Expected signs of mild to moderate peripheral cholinergic stimulation were noted at 0.5 to 1.0 mg doses (q 6 h).(ABSTRACT TRUNCATED AT 250 WORDS)

ANSWER 61 OF 71 MEDLINE on STN

AN 97214656 MEDLINE

DN PubMed ID: 9061036

TI Influence of advanced glycation end-products and AGE-inhibitors on nucleation-dependent polymerization of beta-**amyloid** peptide.

AU Munch G; Mayer S; Michaelis J; Hipkiss A R; Riederer P; Muller R; Neumann A; Schinzel R; Cunningham A M

CS Theodor-Boveri-Institute (Biocenter), Wurzburg, Germany.. muench@biozentrum.uni-wuerzburg.de

SO Biochimica et biophysica acta, **(1997 Feb 27)** 1360 (1) 17-29. Journal code: 0217513. ISSN: 0006-3002.

CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199704

ED Entered STN: 19970422
Last Updated on STN: 19980206
Entered Medline: 19970408

AB Nucleation-dependent polymerization of beta-**amyloid** peptide, the major component of plaques in patients with **Alzheimer**'s disease, is significantly accelerated by crosslinking through Advanced Glycation End-products (AGEs) in vitro. During the polymerization process, both nucleus formation and aggregate growth are accelerated by AGE-mediated crosslinking. Formation of the AGE-crosslinked **amyloid** peptide aggregates could be attenuated by the AGE-inhibitors Tenilsetam, aminoguanidine and carnosine. These experimental data, and clinical studies, reporting a marked **improvement** in **cognition** and memory in **Alzheimer**'s disease patients after Tenilsetam treatment, suggest that AGEs might play an important role in the etiology or progression of the disease. Thus AGE-inhibitors may generally become a promising drug class for the treatment of **Alzheimer**'s disease.

ANSWER 60 OF 71 MEDLINE on STN
AN 97276111 MEDLINE
DN PubMed ID: 9129864
TI Cognitive enhancement therapy for **Alzheimer**'s disease. The way forward.
AU Parnetti L; Senin U; Mecocci P
CS Perugia University, Italy.. parnetti@unipg.it
SO Drugs, **(1997 May)** 53 (5) 752-68. Ref: 107
Journal code: 7600076. ISSN: 0012-6667.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199706
ED Entered STN: 19970709
Last Updated on STN: 19980206
Entered Medline: 19970623
AB Although at present there is no definitive treatment or cure for **Alzheimer**'s disease, different pharmacological strategies are being actively investigated. At present, cholinergic therapy and nootropics and some neuronotrophic agents represent the available approaches to symptomatic treatment of **Alzheimer**'s disease. The use of cholinesterase inhibitors (ChEI) constitutes the best cholinergic approach to increase acetylcholine levels. Available data suggest that about 15 to 40% of **Alzheimer**'s disease patients show a varying degree of **cognitive improvement** while taking these medications; however, haematological complications (neutropenia or agranulocytosis), together with hepatotoxicity, need to be considered carefully. Recent data suggest that long term administration of nootropics may lead to a significant **improvement** of **cognitive** functions in **Alzheimer**'s disease patients compared with untreated individuals, having excellent tolerability. Protocols for the intracerebroventricular administration of neuronotrophic substances are also ongoing. The most promising approaches for the future currently undergoing investigation involve attempts to slow the production of beta-**amyloid** and/or to inhibit beta-**amyloid** aggregation. Another rational therapeutic approach would be to inhibit the formation of paired helical filaments (PHF) by increasing and/or modulating the activities of protein phosphatases and kinases. Antioxidant therapy should disrupt or prevent the free radical/beta-**amyloid** recirculating cascade and the progressive neurodegeneration. Idebenone, a synthetic compound acting as an 'electron trapper' and free radical scavenger, has shown some efficacy in degenerative and vascular dementia; at present, other different molecules having antioxidative properties [lazaroids (21-aminosteroids), pyrrolopyrimidines, nitric oxide blockers, selegiline, some vitamins] are under investigation. Lowering absorption or brain tissue concentrations of aluminium also offers possible therapeutic opportunities for slowing the rate of clinical progression of the disease; in this sense, some evidence exists using the aluminium chelating agent deferoxamine (desferrioxamine). Inflammation also may play a significant pathogenetic role in **Alzheimer**'s disease. As shown by several retrospective analyses, there is an inverse association of anti-inflammatory drug use with the frequency of **Alzheimer**'s disease diagnosis. Consequently, clinical trials using both nonsteroidal and steroidal molecules have been proposed. These lines of pharmacological intervention represent an important premise for future therapeutic strategies capable of counteracting the pathogenesis of **Alzheimer**'s disease.

ANSWER 59 OF 71 MEDLINE on STN
AN 97411970 MEDLINE
DN PubMed ID: 9268083
TI From molecular structure to **Alzheimer** therapy.
AU Giacobini E
CS Department of Geriatrics, University Hospitals of Geneva, University of Geneva, Medical School, Switzerland.
SO Japanese journal of pharmacology, **(1997 Jul)** 74 (3) 225-41.
Ref: 87
Journal code: 2983305R. ISSN: 0021-5198.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199710
ED Entered STN: 19971021
Last Updated on STN: 19980206
Entered Medline: 19971009
AB Clinical trials in the USA, Japan and Europe have confirmed the hypothesis that a steady state increase of acetylcholine resulting from cholinesterase inhibition in the brain results in an **improvement** of **cognitive** function in mild to moderate **Alzheimer** disease (AD) patients. During the last decade, a systematic effort to develop a pharmacological treatment for AD has resulted in two drugs being registered for the first time in the USA and Europe for this specific indication. Both are cholinesterase inhibitors (ChEI). Based on these first positive results, several second generation ChEI are being developed. An additional effect of certain ChEI is to maintain cognitive function at a constant level during a 6 months to one year period of treatment as compared to placebo. It is possible that the drug effect is one of slowing **down** cognitive deterioration. Comparison of clinical effects of 5 ChEI demonstrates a rather similar magnitude of improvement. For some drugs, this may represent a limit, while for others it may be possible to increase the benefit further. To maximize and prolong positive drug effects, it is important to start early and adjust the dosage during the treatment. Other strategies may involve combinations with other cholinergic drugs such as muscarinic or nicotinic agonists. A second important class of drugs which is being developed is that of muscarinic m1 agonists. However, their clinical use is still limited by side effects. The increased knowledge and recognition of the beta-**amyloid** molecule as a central focus of AD pathology has strongly stimulated research with the hope of finding ways of influencing its processing and deposition. At this point, no product in this line of development has reached clinical trial level. Other pharmacological approaches are related to preventive and neuroprotective interventions (estrogens, anti-oxidants and anti-inflammatories). In conclusion, given the relatively short time of research in this field, results are encouraging.

ANSWER 10 OF 13 MEDLINE on STN
AN 97067115 MEDLINE
DN PubMed ID: 8910517
TI Fusogenic properties of the C-terminal domain of the Alzheimer beta-**amyloid** peptide.
AU Pillot T; Goethals M; Vanloo B; Talussot C; Brasseur R; Vandekerckhove J; Rosseneu M; Lins L
CS Laboratory for Lipoprotein Chemistry, Department of Biochemistry, Faculty of Medicine, University Gent, B-9000 Gent, Belgium.
SO Journal of biological chemistry, (1996 Nov 15) 271 (46) 28757-65.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199701
ED Entered STN: 19970128
Last Updated on STN: 19980206
Entered Medline: 19970107
AB A series of natural peptides and mutants, derived from the Alzheimer beta-**amyloid** peptide, was synthesized, and the potential of these peptides to induce fusion of unilamellar lipid vesicles was investigated. These peptide domains were identified by computer modeling and correspond to respectively the C-terminal (e.g. residues 29-40 and 29-42) and a central domain (**13-28**) of the beta-**amyloid** peptide. The C-terminal peptides are predicted to insert in an oblique way into a lipid membrane through their N-terminal end, while the mutants are either parallel or perpendicular to the lipid bilayer. Peptide-induced vesicle fusion was demonstrated by several techniques, including lipid-mixing and core-mixing assays using pyrene-labeled vesicles. The effect of peptide elongation toward the N-terminal end of the entire beta-**amyloid** peptide was also investigated. Peptides corresponding to residues 22-42 and 12-42 were tested using the same techniques. Both the 29-40 and 29-42 beta-**amyloid** peptides were able to induce fusion of unilamellar lipid vesicles and calcein leakage, and the **amyloid** 29-42 peptide was the most potent fusogenic peptide. Neither the two mutants or the **13-28** beta-**amyloid** peptide had any fusogenic activity. Circular dichroism measurements showed an increase of the alpha-helical content of the two C-terminal peptides at increasing concentrations of trifluoroethanol, which was accompanied by an increase of the fusogenic potential of the peptides. Our data suggest that the alpha-helical content and the angle of insertion of the peptide into a lipid bilayer are critical for the fusogenic activity of the C-terminal domain of the **amyloid** peptide. The differences observed between the fusogenic capacity of the **amyloid** 29-40 and 29-42 peptides might result from differences in the degree of penetration of the peptides into the membrane and the resulting membrane destabilization. The longer peptides, residues 22-42 and 12-42, had decreased, but significant, fusogenic properties associated with perturbation of the membrane permeability. These data suggest that the fusogenic properties of the C-terminal domain of the beta-**amyloid** peptide might contribute to the cytotoxicity of the peptide by destabilizing the cell membrane.

L2 ANSWER 11 OF 13 MEDLINE on STN
AN 93208296 MEDLINE
DN PubMed ID: 8457674
TI Structure of beta-crystallite assemblies formed by Alzheimer beta-**amyloid** protein analogues: analysis by x-ray diffraction.
AU Inouye H; Fraser P E; Kirschner D A
CS Children's Hospital, Boston, Massachusetts 02115.
NC AG-08572 (NIA)
HD-18655 (NICHD)

SO Biophysical journal, (1993 Feb) 64 (2) 502-19.
Journal code: 0370626. ISSN: 0006-3495.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199304
ED Entered STN: 19930514
Last Updated on STN: 19930514
Entered Medline: 19930428
AB To elucidate the relation between **amyloid** fibril formation in Alzheimer disease and the primary structure of the beta/A4 protein, which is the major component of the **amyloid**, we have been investigating the ability of peptides sharing sequences with beta/A4 to form fibrils in vitro. In previous studies we focused on the macroscopic morphology of the assemblies formed by synthetic peptides corresponding in sequence to different regions of this protein. In the present study we analyze the x-ray diffraction patterns obtained from these assemblies. All specimens showed wide angle reflections that could be indexed by an orthogonal lattice of beta-crystallites having unit cell dimensions a = 9.4 A, b = 7 A, and c = 10 A, where a refers to hydrogen bonding direction, b to polypeptide chain direction, and c to intersheet direction. Given the amino acid sequence of beta/A4 as NH2-DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIAT-COOH, we found that, based on their orientation and assembly, the analogues could be classified into three groups: Group A, residues 19-28, **13-28**, 12-28, 11-28, 9-28, 1-28, 1-38, 1-40, 6-25, 11-25 and 34-42; Group B, residues 18-28, 17-28, and 15-28; and Group C, residues 22-35 and 26-33. For Groups A and C, the sharpest reflections were (h00), indicating that the assemblies were fibrillar, i.e., elongated in a single direction. Lateral alignment of the crystallites in Group A account for its cross-beta pattern, in which the hydrogen bonding (H-bonding) direction is the fiber (rotation) axis. By comparison, the beta-crystallites of Group C had no preferential orientation, thus giving circular scattering. For Group B, the sharpest reflections were (h01) on the meridian, indicating that the assemblies were plate-like, i.e., extended in two directions. A series of equatorial Bragg reflections having a 40 A period indicated regular stacking of the plates, and the rotation axis was normal to the surface of the plates. Of the Group A peptides, the analogues 11-28 and 6-25 showed intensity maxima on the equator as well as on higher layer lines, indicating that the beta-crystallites are highly ordered relative to one another in the axial, H-bonding direction. This sampling of the layer lines by a larger period (60 A) suggests that the beta-crystallites are arrayed either in cylindrical or small restricted crystalline lattices.(ABSTRACT TRUNCATED AT 400 WORDS)

L2 ANSWER 12 OF 13 MEDLINE on STN
AN 93019227 MEDLINE
DN PubMed ID: 1402902
TI Effects of sulfate ions on Alzheimer beta/A4 peptide assemblies: implications for **amyloid** fibril-proteoglycan interactions.
AU Fraser P E; Nguyen J T; Chin D T; Kirschner D A
CS Children's Hospital, Boston, Massachusetts.
NC AG-08572 (NIA)
HD-18655 (NICHD)
P50-AG05134 (NIA)
SO Journal of neurochemistry, (1992 Oct) 59 (4) 1531-40.
Journal code: 2985190R. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199210

ED Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921026

AB To model the possible involvement of sulfated proteoglycans in **amyloidogenesis**, we examined the influence of sulfate ions, heparan, and Congo red on the conformation and morphology of peptides derived from the Alzheimer beta/A4 **amyloid** protein. The peptides included residues 11-28, **13-28**, 15-28, and 11-25 of beta/A4. Negative-stain electron microscopy revealed a sulfate-specific tendency of the preformed peptide fibrillar assemblies of beta(11-28), beta(**13-28**), and beta(11-25), but not beta(15-28), to undergo extensive lateral aggregation and axial growth into "macrofibers" that were approximately 0.1-0.2 micron wide by approximately 20-30 microns long. Such effects were observed at low sulfate concentrations (e.g., 5-50 mM) and could not be reproduced under comparable conditions with Na2HPO4, Na2SeO4, or NaCl. Macrofibers in NaCl were only observed at 1,000 mM. At physiological ionic strength of NaCl, fibril aggregation was observed only with addition of sulfate ions at 5-50 mM. Selenate ions, by contrast with sulfate ions, induced only axial and not substantial lateral aggregation of fibrils. X-ray diffraction indicated that the original cross-beta peptide conformation remained unchanged; however, sulfate binding did produce an intense approximately 65 A meridional reflection not recorded with control peptides. This new reflection probably arises from the periodic deposition of the electron-dense sulfate along the (long) axis of the fibril. The sulfate binding could provide sites for the binding of additional fibrils that generate the observed lateral and axial aggregation. The binding of heparan to beta(11-28) also produced extensive aggregation, suggesting that in vivo sulfated compounds can promote macrofibers. The **amyloid**-specific, sulfonated dye Congo red, even in the presence of sulfate ions, produced limited aggregation and reduced axial growth of the fibrils. Therefore, electrostatic interactions are important in the binding of exogenous compounds to **amyloid** fibrils. Our findings suggest that the sulfate moieties of certain molecules, such as glycosaminoglycans, may affect the aggregation and deposition of **amyloid** fibrils that are observed as extensive deposits in senile plaques and cerebrovascular **amyloid**.

L2 ANSWER 13 OF 13 MEDLINE on STN
AN 92103138 MEDLINE
DN PubMed ID: 1760507
TI pH-dependent structural transitions of Alzheimer **amyloid** peptides.
AU Fraser P E; Nguyen J T; Surewicz W K; Kirschner D A
CS Neurology Research, Children's Hospital, Boston, Massachusetts.
NC AG-08572 (NIA)
HD-18655 (NICHD)
SO Biophysical journal, (1991 Nov) 60 (5) 1190-201.
Journal code: 0370626. ISSN: 0006-3495.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199202
ED Entered STN: 19920302
Last Updated on STN: 19920302
Entered Medline: 19920213

AB To understand the molecular interactions leading to the assembly of beta/44 protein into the hallmark fibrils of Alzheimer's disease (AD), we have examined the ability of synthetic peptides that correspond to the beta/A4 extracellular sequence to form fibrils over the range of pH 3-10. Peptides included the sequences 1-28, 19-28, 17-28, 15-28, **13-28**, 11-28, and 9-28 of beta/A4. The model fibrils were compared

with isolated **amyloid** with respect to morphology, conformation, tinctorial properties, and stability under denaturing conditions. Electron microscopy, Fourier-transform infrared (FT-IR) spectroscopy, and x-ray diffraction revealed that the ionization states of the amino acid sidechains appeared to be a crucial feature in fibril formation. This was reflected by the ability of several peptides to undergo fibril assembly and disassembly as a function of pH. Comparisons between different beta/A4 sequences demonstrated that the fibrillar structure representative of AD **amyloid** was dependent upon electrostatic interactions, likely involving His-13 and Asp-23, and hydrophobic interactions between uncharged sidechains contained within residues 17-21. The results also indicated an exclusively beta-sheet conformation for the synthetic (and possibly AD fibrils) in contrast to certain other (e.g., systemic) **amyloids**.

L2 ANSWER 4 OF 13 MEDLINE on STN
AN 2001116758 MEDLINE
DN PubMed ID: 11123940
TI SDS-stable complex formation between native apolipoprotein E3 and beta-**amyloid** peptides.
AU Munson G W; Roher A E; Kuo Y M; Gilligan S M; Reardon C A; Getz G S; LaDu M J
CS Department of Pathology, University of Chicago, Chicago, Illinois 60637, USA.
NC AG16776 (NIA)
SO Biochemistry, (2000 Dec 26) 39 (51) 16119-24.
Journal code: 0370623. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200102
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010215
AB Extracellular senile plaques composed predominantly of fibrillar **amyloid**-beta (Abeta) are a major neuropathological feature of Alzheimer's disease (AD). Genetic evidence and in vivo studies suggest that apolipoprotein E (apoE) may contribute to **amyloid** clearance and/or deposition. In vitro studies demonstrate that native apoE2 and E3 form an SDS-stable complex with Abeta(1-40), while apoE4 forms little such complex. Our current work extends these observations by presenting evidence that apoE3 also binds to Abeta(1-42) and with less avidity to modified species of the peptide found in senile plaque cores. These modified peptides include a form that originates at residue 3-Glu as pyroglutamyl and another with isomerization at the 1-Asp and 7-Asp positions. In addition, we used binding reactions between apoE3 and various Abeta fragments, as well as binding reactions with apoE3 and Abeta(1-40) plus Abeta fragments as competitors, to identify the domain(s) of Abeta involved in the formation of an SDS-stable complex with apoE3. Residues **13-28** of Abeta appear to be necessary, while complex formation is further enhanced by the presence of residues at the C-terminus of the peptide. These results contribute to our understanding of the biochemical basis for the SDS-stable apoE3/Abeta complex and support the hypothesis that Abeta can be transported in vivo complexed with apoE. This complex may then be cleared from the interstitial space by apoE receptors in the brain or become part of an extracellular **amyloid** deposit.

L2 ANSWER 5 OF 13 MEDLINE on STN
AN 2000464685 MEDLINE
DN PubMed ID: 11019858
TI Histidine residues underlie Congo red binding to A beta analogs.
AU Inouye H; Nguyen J T; Fraser P E; Shinchuk L M; Packard A B; Kirschner D A
CS Department of Biology, Boston College, Chestnut Hill, MA 02467-3811, USA.
NC P30-AG13846 (NIA)
SO Amyloid : international journal of experimental and clinical investigation : official journal of the International Society of Amyloidosis, (2000 Sep) 7 (3) 179-88.
Journal code: 9433802. ISSN: 1350-6129.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200102
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010208

AB The binding mechanism of Congo red (CR) to Alzheimer's disease (AD) **amyloid** fibrils (A beta) in terms of binding affinity and number of sites was quantitated from absorption spectroscopy (at 200-700 nm) by measuring the concentration of CR bound (CR-B) to AD A beta assemblies as a function of CR concentration and pH in 80% ethanol. The rationale for the use of this high concentration of ethanol derives from its use in histological screens for **amyloid** in tissue sections. Moreover, free CR can be separated from bound CR by filtration in ethanolic but not aqueous medium. The A beta analogs studied here included: (1) peptides having different lengths: A beta1-40, A beta11-28, A beta13-28, A beta19-28, A beta11-25; (2) wildtype, control sequences of A beta1-40 and sequences having different natural amino acid substitutions: primate Pr1-40, rodent Ro1-40, hereditary cerebral haemorrhage with **amyloidosis**, Dutch type (HCHWA-D) Du1-40, primate reverse sequence Pr40-1; and (3) A beta11-25 sequences having different substitutions: H13D, H14D, and D23K. Negative-staining showed that A beta1-40 fibrils in buffer were indistinguishable from those in buffered ethanolic medium. For all **amyloid** analogs except A beta19-28, which has no histidine residues and showed no CR binding over the entire pH range 4.0-9.5, CR-B decreased as a function of increasing pH. The decrease was steepest at about pH 5 and became zero above pH 7. For analogs having the same number of histidines, CR-B fell on the same binding curve, indicating that histidine residues are the likely binding sites for CR in this medium. The pH titration of the binding was parameterized by the stoichiometry of dye to the sites, the number of histidines per molecule, the binding dissociation constant Kd, and the apparent proton dissociation constant pK of the histidine; and the calculated pH-titration curves were found to fit the observed ones. For the peptides having 1-3 histidines the average pK was 5.0-5.5, which was similar to the expected pK of histidine in low dielectric medium (80% ethanol), and the Kd's were 2.8-5.9 microM. That histidine residues underlie CR binding in A beta **amyloid** is consistent with previous findings that A beta peptides sediment as fibrillar assemblies at pH-3-7 and bind Congo red over the same pH range in aqueous medium. Further, the conformation near the binding motif His13-His14-Gln15-Lys16 in A beta assemblies is not greatly altered in 80% ethanol.

L2 ANSWER 6 OF 13 MEDLINE on STN
AN 1999429317 MEDLINE
DN PubMed ID: 10501209
TI The nonfibrillar **amyloid** beta-peptide induces apoptotic neuronal cell death: involvement of its C-terminal fusogenic domain.
AU Pillot T; Drouet B; Queille S; Labeur C; Vandekerchkhove J; Rosseneu M; Pincon-Raymond M; Chambaz J
CS INSERM U-505, Institut des Cordeliers, Paris, France.
SO Journal of neurochemistry, (1999 Oct) 73 (4) 1626-34.
Journal code: 2985190R. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991014
AB The toxicity of the nonaggregated **amyloid** beta-peptide (1-40) [A beta(1-40)] on the viability of rat cortical neurons in primary culture was investigated. We demonstrated that low concentrations of A beta peptide, in a nonfibrillar form, induced a time- and dose-dependent apoptotic cell death, including DNA condensation and fragmentation. We compared the neurotoxicity of the A beta(1-40) peptide with those of several A beta-peptide domains, comprising the membrane-destabilizing C-terminal domain of A beta peptide (e.g., amino acids 29-40 and 29-42).

These peptides reproduced the effects of the (1-40) peptide, whereas mutant nonfusogenic A beta peptides and the central region of the A beta peptide (e.g., amino acids **13-28**) had no effect on cell viability. We further demonstrated that the neurotoxicity of the nonaggregated A beta peptide paralleled a rapid and stable interaction between the A beta peptide and the plasma membrane of neurons, preceding apoptosis and DNA fragmentation. By contrast, the peptide in a fibrillar form induced a rapid and dramatic neuronal death mainly through a necrotic pathway, under our conditions. Taken together, our results suggest that A beta induces neuronal cell death by either apoptosis and necrosis and that an interaction between the nonfibrillar C-terminal domain of the A beta peptide and the plasma membrane of cortical neurons might represent an early event in a cascade leading to neurodegeneration.

L2 ANSWER 1 OF 13 MEDLINE on STN
AN 2005107930 MEDLINE
DN PubMed ID: 15706615
TI Hydrolysis of the **amyloid** beta-peptide (A beta) 1-40 between Asp23-Val24 produces non-aggregating fragments. An electrospray mass spectrometric study.
AU Hosia Waltteri; Griffiths William J; Johansson Jan
CS Department of Medical Biochemistry and Biophysics, Karolinska Institutet, S-171 77 Stockholm, Sweden.
SO Journal of mass spectrometry : JMS, (2005 Feb) 40 (2) 142-5.
Journal code: 9504818. ISSN: 1076-5174.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200504
ED Entered STN: 20050302
Last Updated on STN: 20050407
Entered Medline: 20050406
AB The aggregation of full-length (residues 1-40) **amyloid** beta-peptide (A beta) and fragments corresponding to residues 1-23 and 24-40 was studied by electrospray mass spectrometry, using gramicidin as a non-aggregating reference. Following a lag period, A beta(1-40) at 140 microM concentration aggregates with apparent first-order kinetics. Under acidic conditions A beta(1-40) undergoes spontaneous cleavage between Asp23-Val24 and to a lesser extent also at two other Asp-X motifs. Incubation in acidic H(2)18O showed incorporation of 18O in fragment A beta(1-23), confirming that the Asp23-Val24 peptide bond had been hydrolyzed. Incubation of synthetic A beta(1-23) and A beta(24-40) peptides with A beta(1-40) showed that A beta(24-40) remained in solution for several months, that A beta(1-23) partly disappeared from solution, whereas A beta(1-40) completely disappeared. Further, treatment of sedimentable aggregates formed after co-incubation of the three peptides with hexafluoro-2-propanol or formic acid recovered the intensity of A beta(1-40). These data support previous studies showing that the region of A beta encompassing residues **16-24** is necessary for aggregation into **amyloid** fibrils.

L2 ANSWER 2 OF 13 MEDLINE on STN
AN 2004003007 MEDLINE
DN PubMed ID: 14698294
TI Effect of different anti-Abeta antibodies on Abeta fibrillogenesis as assessed by atomic force microscopy.
AU Legleiter Justin; Czilli Dan L; Gitter Bruce; DeMattos Ronald B; Holtzman David M; Kowalewski Tomasz
CS Department of Chemistry, Carnegie Mellon University, 4400 Fifth Avenue, Pittsburgh, PA 15213, USA.
NC AG05681 (NIA)
AG20222 (NIA)
SO Journal of molecular biology, (2004 Jan 23) 335 (4) 997-1006.
Journal code: 2985088R. ISSN: 0022-2836.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200402
ED Entered STN: 20040106
Last Updated on STN: 20040211
Entered Medline: 20040210
AB Extensive data suggest that the conversion of the **amyloid**-beta (Abeta) peptide from soluble to insoluble forms is a key factor in the

pathogenesis of Alzheimer's disease (AD). In recent years, atomic force microscopy (AFM) has provided useful insights into the physicochemical processes involving Abeta morphology, and it can now be used to explore factors that either inhibit or promote fibrillogenesis. We used ex situ AFM to explore the impact of anti-Abeta antibodies directed against different domains of Abeta on fibril formation. For the AFM studies, two monoclonal antibodies (m3D6 and m266.2) were incubated in solution with Abeta(1-42) with a molar ratio of 1:10 (antibody to Abeta) over several days. Fibril formation was analyzed quantitatively by determining the number of fibrils per microm(2) and by aggregate size analysis. m3D6, which is directed against an N-terminal domain of Abeta (amino acid residues 1-5) slowed down fibril formation. However, m266.2, which is directed against the central domain of Abeta (amino acid residues **13-28**) appeared to completely prevent the formation of fibrils over the course of the experiment. Inhibition of fibril formation by both antibodies was also confirmed by thioflavin-T (ThT) fluorescence experiments carried out with Abeta(1-40) incubated for five days. However, unlike AFM results, ThT did not differentiate between the samples incubated with m3D6 versus m266.2. These results indicate that AFM can be not only reliably used to study the effect of different molecules on Abeta aggregation, but that it can provide additional information such as the role of epitope specificity of antibodies as potential inhibitors of fibril formation.

ANSWER 10 OF 22 MEDLINE on STN

AN 2002177656 MEDLINE

DN PubMed ID: 11910111

TI Brain to plasma **amyloid**-beta efflux: a measure of brain **amyloid** burden in a mouse model of Alzheimer's disease.

AU DeMattos Ronald B; Bales Kelly R; Cummins David J; Paul Steven M; Holtzman David M

CS Center for the Study of Nervous System Injury, Alzheimer's Disease Research Center, Department of Neurology, Molecular Biology and Pharmacology, Washington University School of Medicine, 660 South Euclid Avenue, Box 8111, St. Louis, MO 63110, USA.

NC AG20222 (NIA)

SO Science, (2002 Mar 22) 295 (5563) 2264-7.
Journal code: 0404511. ISSN: 1095-9203.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200204

ED Entered STN: 20020324
Last Updated on STN: 20020405
Entered Medline: 20020404

AB The deposition of **amyloid**-beta (Abeta) peptides into **amyloid** plaques precedes the cognitive dysfunction of Alzheimer's disease (AD) by years. Biomarkers indicative of brain **amyloid** burden could be useful for identifying individuals at high risk for developing AD. As in AD in humans, baseline plasma Abeta levels in a transgenic mouse model of AD did not correlate with brain **amyloid** burden. However, after peripheral administration of a monoclonal antibody to Abeta (**m266**), we observed a rapid increase in plasma Abeta and the magnitude of this increase was highly correlated with **amyloid** burden in the hippocampus and cortex. This method may be useful for quantifying brain **amyloid** burden in patients at risk for or those who have been diagnosed with AD.

ANSWER 9 OF 22 MEDLINE on STN

AN 2002238960 MEDLINE

DN PubMed ID: 11941374

TI Immunization reverses memory deficits without reducing brain Abeta burden in Alzheimer's disease model.

AU Dodart Jean-Cosme; Bales Kelly R; Gannon Kimberley S; Greene Stephen J; DeMattos Ronald B; Mathis Chantal; DeLong Cynthia A; Wu Su; Wu Xin; Holtzman David M; Paul Steven M

CS Neuroscience Discovery Research, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, USA.

SO Nature neuroscience, (2002 May) 5 (5) 452-7.
Journal code: 9809671. ISSN: 1097-6256.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200205

ED Entered STN: 20020429
Last Updated on STN: 20020514
Entered Medline: 20020513

AB We have previously shown that chronic treatment with the monoclonal antibody **m266**, which is specific for **amyloid** beta-peptide (Abeta), increases plasma concentrations of Abeta and reduces Abeta burden in the PDAPP transgenic mouse model of Alzheimer's disease (AD). We now report that administration of **m266** to PDAPP mice can rapidly reverse memory deficits in both an object recognition task and a holeboard learning and memory task, but without altering brain Abeta burden. We also found that an Abeta/antibody complex was present in both the plasma and the cerebrospinal fluid of **m266**-treated mice. Our data indicate that passive immunization with this anti-Abeta monoclonal antibody can very rapidly reverse memory impairment in certain learning and memory tasks in the PDAPP mouse model of AD, owing perhaps to enhanced peripheral clearance and (or) sequestration of a soluble brain Abeta species.

ANSWER 1 OF 22 MEDLINE on STN

AN 2005041549 MEDLINE

DN PubMed ID: 15659599

TI Exacerbation of cerebral **amyloid** angiopathy-associated microhemorrhage in **amyloid** precursor protein transgenic mice by immunotherapy is dependent on antibody recognition of deposited forms of **amyloid** beta.

AU Racke Margaret M; Boone Laura I; Hepburn Deena L; Parsadainian Maia; Bryan Matthew T; Ness Daniel K; Piroozi Kathy S; Jordan William H; Brown Donna D; Hoffman Wherly P; Holtzman David M; Bales Kelly R; Gitter Bruce D; May Patrick C; Paul Steven M; DeMattos Ronald B

CS Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285, USA.

SO Journal of neuroscience : official journal of the Society for Neuroscience, (2005 Jan 19) 25 (3) 629-36.
Journal code: 8102140. ISSN: 1529-2401.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200508

ED Entered STN: 20050127
Last Updated on STN: 20050819
Entered Medline: 20050818

AB Passive immunization with an antibody directed against the N terminus of **amyloid** beta (Abeta) has recently been reported to exacerbate cerebral **amyloid** angiopathy (CAA)-related microhemorrhage in a transgenic animal model. Although the mechanism responsible for the deleterious interaction is unclear, a direct binding event may be required. We characterized the binding properties of several monoclonal anti-Abeta antibodies to deposited Abeta in brain parenchyma and CAA. Biochemical analyses demonstrated that the 3D6 and 10D5, two N-terminally directed antibodies, bound with high affinity to deposited forms of Abeta, whereas **266**, a central domain antibody, lacked affinity for deposited Abeta. To determine whether **266** or 3D6 would exacerbate CAA-associated microhemorrhage, we treated aged PDAPP mice with either antibody for 6 weeks. We observed an increase in both the incidence and severity of CAA-associated microhemorrhage when PDAPP transgenic mice were treated with the N-terminally directed 3D6 antibody, whereas mice treated with **266** were unaffected. These results may have important implications for future immune-based therapeutic strategies for Alzheimer's disease.